Remarks

The Examiner rejected Claims 1, 3-7, 9, 24-26 under 35 USC 112, first paragraph as failing to comply with the written description requirement. Specifically, the Examiner asserted that the specification does not describe a representative number of species in the genus of nuclear steroid receptors capable of binding *single stranded* polynucleotides. The Examiner contends that the skilled artisan could not immediately envisage what other species in the genus of nuclear steroid receptors would be capable of binding single stranded DNA. Applicant respectfully traverses this rejection and requests reconsideration of this rejection in light of the following:

Prior to the filing date of this application, those of ordinary skill in the art were well aware that nuclear steroid receptors were capable of binding single stranded DNA. Exemplary reporting of such binding to single stranded DNA appears in the scientific articles listed below, all of which were published and in the literature long prior to the effective filing date of this application. These articles are relevant to the patentability of the claims as issue in that the articles demonstrate the widespread knowledge in the field that nuclear strand receptors could bind single stranded DNA; hence the description and claims necessarily comport with 35 USC 112.[1]

Hughes MR et al., Biochemistry, 1981 20(9):2481-91
"Interaction of the chick oviduct progesterone receptor with deoxyribonucleic acid"

Franceschi., Proc Natl Acad Sci USA, 1984 81(8):2337-41
"Interaction of the 1 alpha, 2,5-dihydroxyvitamin D3 receptor with RNA and synthetic polyribonucleotides"

Lin SY et al., Biochim, Biophys Acta 1981 654(2):181-6
"The binding of androgen receptor to DNA and RNA"

[1] The listed articles are not otherwise believed to be relevant or material to the 35 USC § 102 or § 103 patentability of the claims.

Abstracts of these articles are attached to the accompanying Information Disclosure Statement.

Thus, it was known long before the priority date of this application that the progesterone receptor, androgen receptor and vitamin D3 receptor were all able to bind to single stranded DNA. This application specifically refers to the progesterone receptor on page 9, line 9; page 11, line 10 and page 16, line 7 of the description.

Moreover, procedures for establishing whether or not a nuclear steroid receptor was capable of binding to single stranded DNA were well established and well known long before the priority date of this application. Published methodologies appearing long before the earliest effective filing date for this application and suitably describing such procedures include:

Norby et al., Nucleic Acid Res 1992 20(23): 6317-21
"Determination of recognition-sequences for DNA-binding proteins by a polymerase chain reaction assisted binding site selection method (BSS) using nitrocellulose immobilized DNA binding protein"

Pierrou et al., Anal Biochem 1995 229(1):99-105
"Selection of high affinity binding sites for sequence-specific, DNA binding proteins from random sequence oligonucleotides"

Sozeri et al., Nucleic Acid Res 1992 20(9):2257-63
"Determination of the DNA sequence recognized by the bHLH-zip domain of the N-Myc protein"

Thiesen et al., Nucleic Acid Res 1990 18(11):3203-9
"Target Detection Assay (TDA): a versatile procedure to determine DNA binding sites as demonstrated on SP1 protein"

Wright et al., Mol Cell Biol 1991 11(8):4104-10
"Cyclic amplification and selection of targets (CASTing) for the myogenin consensus binding site"

Abstracts of these articles are also attached to the accompanying Information Disclosure Statement.

Thus, those of ordinary skill in the art would have the knowledge, ability, and capability of determining whether a member of the nuclear steroid receptor family was able to bind single stranded DNA, using these well-known and long established procedures and protocols. Clearly it was already known that nuclear steroid receptors were capable of binding single stranded DNA as indicated above in Hughes et al., Franchesi, and Lin et al., and as disclosed in the application.

The Examiner rejected Claims 1, 4-7, 9, 24-25 under 35 USC 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which the applicant regards as the invention. Applicant traverses this rejection and requests reconsideration in light of the amendment of claims 1, 24 and 25 to specify that the binding moiety is a viral protein.

Claims 1, 3-7, 9, 24-26 were rejected under 35 USC 103(a) as being unpatentable over Rebar et al., in view of Lannigan et al. Applicant traverses this rejection and requests reconsideration in view of the following:

Rebar et al. teaches use of filamentous phage to display zinc finger proteins attached to the pIII coat protein. A construct is produced expressing a chimeric pIII-zinc finger protein. The phage itself contains a single stranded genome. The zinc finger element of the chimeric protein is able to bind to specific DNA sequence motifs.

Lannigan et al. teaches that the estrogen receptor binds preferentially to the coding strand of the estrogen response element.

The Examiner asserts that it would have been obvious to one of ordinary skill in the art to use the coding strand and estrogen receptor of Lannigan et al. with the phage display system of Rebar et al.

However, replacing the zinc finger element of the Rebar et al., construct with the estrogen receptor of Lannigan et al., would not produce nor render obvious the construct of the present invention.

The construct taught by Rebar et al. lacks a number of fundamental structural features now specified in the claims; these features would not be introduced by replacing the zinc finger of the Rebar et al. construct by the estrogen receptor.

First, Rebar et al. selects only for specific zinc finger proteins able to bind to "desired target sites on double stranded DNA" (see Abstract, last line). Indeed Rebar et al. makes numerous references to this effect, referring to "target DNA duplexes" (page 671, second column, lines 12-13), "biotinylinated DNA duplexes" (page 672, legend to Figure 1D), "three DNA duplexes" (page 672, legend to Table 3) and in concluding asks (but does not answer) whether it is "possible to select a zinc finger peptide that recognizes any desired sequence on *double-stranded* DNA" (page 673, column 1, lines 16-18, emphasis added.) Nowhere does Rebar et al. refer to zinc fingers binding to single stranded DNA. One of ordinary skill in the art would not consider use of a *single stranded* target DNA sequence (as specified in applicant's claims), given the speculation by Rebar et al. that it might be possible to use double stranded DNA as a target sequence.

Second, given that Rebar et al., teaches binding of the zinc fingers to double stranded DNA, it is clear that in the construct of Rebar et al. the polynucleotide binding portion of the chimeric protein (i.e. the zinc finger) does not bind to the single stranded polynucleotide <u>forming part of</u> the construct (i.e. the phage genome) as is required in the present claims. Claims 1, 24 and 25 each require that the nucleotide binding portion of the chimeric protein <u>is bound</u> to the recombinant polynucleotide,

and the claims specify that the recombinant polynucleotide is single stranded. In Rebar et al., the zinc finger portion is not bound to the polynucleotide of the construct, and is also unable to bind single stranded DNA, as required in the claims. Instead the construct of Rebar et al. binds to externally presented target DNA duplexes. See page 671, second column, paragraph 2, stating that:

> "Affinity selection methods were then used to search the library for phage that would recognize altered binding sites. In each round of affinity selection, phage were equilibrated with biotinylated target DNA and then applied to streptavidin-coated microtiter wells." (Emphasis added)

Thus the target DNA of Rebar et al. was labeled with biotin and was separate and distinct from the genome of the phage construct. Contrasting, the present claims require that the polynucleotide is bound specifically by the polynucleotide binding portion of the chimeric protein and also encodes for the chimeric protein itself. This dual role of the polynucleotide is nowhere suggested within Rebar et al. or Lannigan et al. The teaching of Lannign et al. does not cure this deficiency.

Rebar et al. does not produce or suggest a PDCP in which the chimeric protein is simultaneously bound to a single stranded recombinant polynucleotide forming part of the construct via a specific nucleotide binding portion whilst being expressed on the surface of the package. Indeed, the pIII protein of the chimeric protein of the Rebar et al. construct is not known to bind polynucleotide. In filamentous phage the pIII coat protein is a minor component of the coat, the majority of which is composed of the pVIII coat protein. There are generally only 5 copies of the pIII protein per phage, located at one end of the phage. Rebar et al. acknowledges the limitation afforded by use of the pIII protein in terms of the number of fusion proteins that can be expressed – see the legend of Figure 1B.

Thus, merely replacing the zinc finger portion of the construct of Rebar et al. with the estrogen receptor of Lannigan et al., would not produce a construct where the

polynucleotide recognized by the estrogen receptor (the ERE) also includes a coding region for the chimeric protein itself, since this feature is not taught or suggested in either Rebar et al. or Lannigan et al. The claims clearly require the polynucleotide of the complex to have "a nucleotide sequence motif which is specifically bound by said nucleotide binding portion of the chimeric protein".

The claims remaining in the application are believed to be in condition for allowance. An early action toward that end is earnestly solicited.

A Petition for an Extension of time is submitted herewith.

To the extent there is any additional fee required in connection with the receipt, acceptance and/or consideration of this paper and/or any accompanying papers submitted herewith, please charge all such fees to Deposit Account 50-1943.

Respectfully submitted,

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BY: Gayle Ruckstuhl

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